Missing data in survival analyses

Nicola Schmitt, AstraZeneca

Acknowledgements: Andrew Stone, Euan Macpherson
AstraZeneca
Nicola Schmitt is an employee of AstraZeneca LP. The views and opinions expressed herein are her own and cannot and should not necessarily be construed to represent those of AstraZeneca or its affiliates.
Missing data and Censoring

• At the end of the trial the event of interest may not have been observed
• The patient is censored in the analysis; this is a form of missing data
• There is a sense amongst some investigators that when we censor a patient in the analysis, it solves all the problems
• However traditional survival analysis techniques assume patients are censored at random
• Dependent/informative censoring is problematic to the results and interpretation
Dependent (informative) Censoring

- Censored subjects are either more or less likely to experience the specific event in the future.

- In particular, this arises if covariates affect both probability of event and probability of being censored.

- Example
  - Symptoms of Disease
    - Probability of Drop-out
    - Probability of Disease Progression

- Data is not missing completely at random.
Examples of censoring that may be dependent (informative)

- Blinded independent central review data is missing (investigator thinks patient has progressed and stops further scans. Retrospective BICR does not agree)
- Patients take an alternative therapy prior to progression
- Analysis of overall survival and cross-over to experimental therapy at the point of disease progression
- Patients drop out prior to objective progression because of improvement, or worsening
- Time to symptom deterioration – patient progresses radiologically but without symptoms, data collection stopped
Censoring rules impact trial conduct

• Accepted approach for overall survival is to follow all patients to death

• This approach has been advocated for PFS\(^1\)
  - Concern re bias from informative censoring otherwise

• Different approaches also advocated e.g. censor at time of subsequent therapy\(^2\)

---


Missing data has been a discussion point for Oncology drug advisory committees (ODACs)

Avastin (breast) ODAC 2010
‘The review team did not have confidence in the PFS results because baseline or PFS-determining radiographic scans were missing in 10% of the patients and 34% of the patients were not followed until an IRRC-determined PFS event or the end of the study. …..patients could be offered false hope’

Xgeva (prostate) ODAC 2010
‘A post-hoc exploratory analysis of time to symptomatic bone metastasis, which may be considered a more relevant measure of clinical benefit in this setting, is of limited value due to missing data since most patients were not followed until they experienced the first symptomatic metastasis.’
Missing data can lead to bias
Censoring analyses co-ordinated by the PhRMA PFS expert team

• 26 trials from 12 companies/institutions re-analysed trials using pre-specified SAP for 5 analyses

  • **Analysis 1- ITT Approach (ITT)**
    • actual date of progression or death used in the analysis

  • **Analysis 2- Censor for subsequent therapy (PDT)**
    • any patient who starts other anti-cancer therapy prior to progressing

  • **Analysis 3- Censor at treatment discontinuation due to toxicity and other, non-progression related reasons (DISC)**

  • **Analysis 4- Censor missed visits (MV)**
    • patients who progress or die after ≥2 consecutive missed visits

  • **Analysis 5- Combined censoring (ALL)**
    • censored at earliest censoring time of analyses 2 to 4

*Denne et Al, J Biopharm Stats 2013 23 951-970*
Effect on events/follow-up from censoring rules

<table>
<thead>
<tr>
<th>Censor</th>
<th>Median Percentage of ITT Events Censored</th>
<th>Median Percentage Reduction in Follow-up</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Control</td>
<td>Experimental</td>
</tr>
<tr>
<td>Subsequent Anti-Cancer Therapy (PDT)</td>
<td>9%</td>
<td>8%</td>
</tr>
<tr>
<td>Withdrawal Due to Toxicity /Other non PD reason (DISC)</td>
<td>16%</td>
<td>17%</td>
</tr>
<tr>
<td>Two or more Consecutive Missed Visits (MV)</td>
<td>5%</td>
<td>7%</td>
</tr>
<tr>
<td>All of the above (ALL)</td>
<td>23%</td>
<td>23%</td>
</tr>
</tbody>
</table>

On average,
- Censoring discontinuations led to censoring the most events
- Censoring was similar across arms
- Censoring ‘ALL’ led to around one quarter of events being censored

*Denne et Al, J Biopharm Stats 2013 23 951-970*
Differential Informative Censoring (IC)

- Metric defined to represent a measure of degree of IC
- Calculate the Censored Event Rate Ratio (CERR) for each arm
  - CERR = event rate* before censoring / event rate after censoring
  - If ratio ≠ 1 then evidence of IC within arm
- Ratio(exp/control) of CERR calculated and used as measure of differential IC
- Example: CERR = 2 in exp and 1.5 in control, CERR ratio > 1
  - Would expect experimental to be favoured (in censored analysis) as worse group of experimental patients ‘excluded’ from censoring

* Event rate = no. of events/total patient follow-up

Denne et Al, J Biopharm Stats 2013 23 951-970
Effect of Differential Informative Censoring

If censoring is related to prognosis in at least one arm AND the extent of IC was higher in exp. arm – then exp. arm favoured by censored analysis

Conclusion from PhRMA work
You need both censoring that is informative and its rate to differ between arms to get bias

Note:
- 95 data points (9 missing due to not estimable rates)
- Two x-values >3 and <5 truncated at 3; no impact on slope
Pharma Recommendations

• Follow all patients to progression
  - Regardless of whether they stop randomised therapy or start new anti-cancer therapy

• ITT for the primary analysis
  - It is the most conservative
  - Perform supportive analyses which censor on a new anti-cancer therapy
  - The rate of patients who are lost to follow-up should be summarised by treatment arm, both overall and by important prognostic factors
Strategies for dealing with missing data
Strategies for handling missing data

Focus on prevention is key

If all else fails, perform sensitivity analyses:

1) Simple summaries
2) Simple analyses which assign censored patients as events
3) More sophisticated analyses (e.g. multiple imputation methods)
Prevention – some practical steps we can take to minimise missing data

- **Survival**: Include in patient consent form that public records can be used to determine date of death
- **PFS**: Plan in protocol to scan until objective progression, irrespective of treatment discontinuation, change of therapy etc
- **Review metrics during study in a blinded fashion and act on problems**
  - (e.g. number of patients who withdraw prior to progression)
Sensitivity analyses (1)

Simple summaries

• Example: missing survival data

• Create a KM plot of time to censoring:
  - An imbalance in patients lost to follow-up could be indicative of bias
  - Similar KM lines indicate similar rates of censoring on each arm

• Summary of censored subjects by time and key baseline factors:
  - The key baseline data should be balanced between the treatment arms for both subjects censored early (e.g. >3m prior to DCO) and late
  - Could also stratify the KM plot of time to censoring by important prognostic categorical variables
Conclusion: Time to censoring was comparable between the two treatment groups.
Sensitivity analyses (2)

Example: Assign events to censored patients

• Trial of vandetanib 300mg vs placebo (n=331)
• PFS Hazard ratio=0.46 (95% CI 0.31-0.69) based on blinded independent central review
• 8% vandetanib, 7% placebo progressed by investigator but not by central review >3 months prior to data cut-off
• Censoring of such patients is likely to be informative (Dodd 2008)

• Sensitivity analysis: assumed an event would have occurred according to the central review at the next scheduled visit
• Results for sensitivity analysis: HR=0.51 (95% CI 0.36-0.74)
Sensitivity analyses (3)


Example

- Primary endpoint: progression free survival
- Secondary endpoint: time to symptom progression
  - Based on patient reported outcome (PRO) data
  - Patient not followed for PRO after radiologic progression
  - Informative censoring likely: would expect radiologic progression to lead to symptom progression

- What imputation method will allow us to get closer to the truth when large amounts of informative censoring prior to DCO?
One possible approach to get closer to truth in analysing time to symptom progression:

- For patients censored – impute a time to event based on “similar” patients with time to event ≥ censored time
- Similar patients - nearest neighbours in terms of risk score for censoring or event of interest
- Risk scores from cox models of time to censoring or time to event with appropriate time dependent covariates
- Eg rate of change in symptom score
- Use Kaplan-Meier imputation to impute a new event time
- Process is repeated for each censored subject
- Analyse data with imputed times to estimate HR adjusted for the presence of informative censoring
Kaplan-Meier Imputation Method

- From NN neighbours, use Kaplan-Meier imputation (KMI) method to read off imputed TTE and censoring indicator

- Generate random number between 0 and 1 using uniform distribution
- Read off KM and impute value for subject i
  - E.g. TTE=12.78 mo, event
- Nb. Imputed time shouldn’t be more than data cut-off date

Recovery of Truth In Analysis Of Time To Worsening In LCS Data
Output from Cox Analyses and Multiple Imputation Method
Recovery of Truth In Analysis Of Time To Worsening In LCS Data

• The hazard ratio returned for the analysis of each test data set is closer to the Truth using the multiple imputation approach vs. the standard cox analysis

• Suggests that the auxiliary variable of rate of change in LCS was of use in determining nearest neighbours for Kaplan-Meier imputation
Summary

Dependent censoring can be problematic to analysis and interpretation of data.

Our focus should be on prevention.

If all else fails, sensitivity analyses should be performed.

1) Simple summaries
2) Simple analyses which assign censored patients as events
3) More sophisticated analyses such as multiple imputation
References


FDA Guidance for Industry Clinical Trial Endpoints for the Approval of Cancer Drugs and Biologics. (2007)


Oncologic Drugs Advisory Committee (ODAC) Meeting Briefing Document, 02 December 2010

Confidentiality Notice

This file is private and may contain confidential and proprietary information. If you have received this file in error, please notify us and remove it from your system and note that you must not copy, distribute or take any action in reliance on it. Any unauthorized use or disclosure of the contents of this file is not permitted and may be unlawful. AstraZeneca PLC, 2 Kingdom Street, London, W2 6BD, UK, T: +44(0)20 7604 8000, F: +44 (0)20 7604 8151, www.astrazeneca.com
• Randomly re-sample with replacement
• Re-sampled data has same number of observations as the original data in each treatment group

28 Nicola Schmitt | November 2013
For censored patients in Trt A

- Nearest neighbours
  - those patients who ‘behave’ most like the censored patient of interest at the time that patient was censored
    - ‘behave’ – prognostic and time dependent covariates
  - selected from those patients who are ‘at risk’ of the event beyond the censored patient of interest